REMARKS

These remarks are in response to the Final Office Action mailed December 28, 2004. Claims 1, 3, 9 and 10 are pending. Claim 1 is amended herein to more clearly describe the claimed subject matter. Basis for the amendment can be found in the specification as originally filed (see for example, pages 2-3, and Examples 5 and 6). Claims 2, 4-8, and 11-26 are canceled herein without prejudice or disclaimer. Applicant reserves the right to prosecute the canceled subject matter in any divisional, continuation, continuation-in-part or other application. No new subject matter has been introduced.

Rejection under 35 U.S.C. § 102

Claims 1, 3, 9 and 10 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Hall *et al.* (WO 98/44938). Applicant respectfully traverses this rejection.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and

unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Independent claim 1, as amended herein, is directed to a targeted retroviral vector particle comprising a modified viral surface protein for targeting the vector to the extracellular matrix or tumor vasculature of a tumor, the modified viral surface protein comprising a von Willebrand factor collagen binding motif, and a cytokine gene that encodes GM-CSF, wherein wherein cells of the tumor transduced by the vector express GM-CSF, resulting in the recruitment of host mononuclear cells to the site of the tumor. Dependent claim 2 specifies the modified retroviral surface protein for targeting extracellular matrix. Dependent claims 9 and 10 are directed to a pharmaceutical composition comprising the retroviral vector particle and a method for cancer treatment via intravenous adminstration of the pharmaceuctical composition.

The Disclosure of Hall *et al.* (WO 98/44398)

The Office Action alleges that Hall *et al.* discloses a retroviral particle wherein the viral surface protein has been modified to include a targeting polypeptide that binds to extraceullar matrix components and that the particle also comprises a therapeutic gene. Hall *et al.* allegedly discloses the targeting polypeptide to include a collagen binding domain such as present in von Willebrand collagen factor. It is also alleged that Hall *et al.* disclose that the therapeutic gene present in the vector can be any gene, such as a cytokine, including GM-CSF, and that the art also teaches method of delivery of the therapeutic genes to tumors and a method of treatment.

Differences between the claims and the disclosure of Hall *et al.*

Hall *et al.* discloses a viral vector particle having a modified viral surface protein wherein the viral surface protein is modified to include a targeting polypeptide which binds to an extracellular matrix component. Hall *et al.* discloses a modified retroviral targeting polypeptide comprising the collagen-binding domain of von Willebrand factor. Hall *et al.* also discloses a therapeutic gene encoded by the viral particle, including a cytokine such as GM-CSF, and methods of delivery and treatment of diseases and disorders associated with exposed extracellular matrix components, including cancer.

Hall *et al.* does not disclose a targeted retroviral particle comprising a modified surface protein for targeting extracellular matrix or tumor vasculature of a tumor and a gene encoding GM-CSF for transducing cells of a tumor, wherein expression of GM-CSF results in recruitment of host mononuclear cells to the site of the tumor.

Analysis

Hall *et al.* does not anticipate claim 1 as amended herein, nor any claims dependent thereon. Claim 1 as amended herein, includes the element of recruiting host mononuclear cells to the site of a tumor as the result GM-CSF expression from tumor cells transduced with a targeted retroviral particle comprising a modified surface protein for targeting to the extracellular matrix or tumor vasculature of a tumor and a gene encoding GM-CSF. Hall *et al.* fails to disclose a targeted retroviral particle comprising a modified surface protein including a von Willebrand factor collagen binding motif and a gene encoding GM-CSF for transducing cells of a tumor and recruiting host mononuclear cells to the site of tumor in response to expression of GM-CSF.

The Examiner indicated in the "Response to Arugement" in the Final Office Action mailed December 28, 2004, that Applicants have argued the un-expected result of recruitment of host mononuclear cells to the site of tumor upon administration of the targeting vector encoding GM-CSF to the animal. The Examiner also indicated that this result is irrelevant to the pending claims as filed on October 25, 2004, because no such limitation is recited in the claims. As amended herein, claim 1 now recites the limitation of recruiting host mononuclear cells to the

site of tumor as a result of GM-CSF expression from cells of a tumor transduced by a retroviral vector particle comprising a modified surface protein for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a cytokine gene, as setforth by the Examiner.

Therefore, since anticipation requires that a reference disclose all elements as claimed, Hall *et al.*, which does not disclose a targeted retroviral vector comprising a surface protein that includes a von Willebrand factor collagen binding motif and gene encoding GM-CSF for transduction of a tumor wherein host mononuclear cells are recruited to the site of the tumor upon expression of GM-CSF, does not disclose each element as claimed. Thus, Hall *et al.* does not anticipate claim 1 as amended herein, nor any of dependent claims 3, 9 and 10.

Rejection under 35 U.S.C. § 103

Claims 1, 3, 9 and 10 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hall *et al.* (WO 98/44938; refered to as Hall-1, hereafter) or Hall *et al.* (Human Gene Therapy 11:983-993 (2000); refered to as Hall-2, hereafter) or Liu *et al.* (Journal of Virology 74:5320-5328(2000) or Gordon *et al.* (Cancer Research 60:3343-3347 (2000)) in view of Kurane *et al.* (Annals of Surgery 4:579-585(1997)) and Borrello *et al.* (Human Gene Therapy 10: 1983-1991(1999)) for reasons of record set forth in the previous office action of 8/21/03 and 5/18/04.

The Examiner alleges that at the time of the invention, it would have been obvious to an artisan of skill to modify the vector(s) of Hall-1, Hall-2, Liu *et al.* or Gordon *et al.* by cloning the GM-CSF encoding sequences taught by Borrello *et al.* with a resonable expectation of success and use the resultant vector for delivering GM-CSF to a tumor in an animal. The Examiner also alleges that an artisan would have been motivated to make such a vector because Borrello *et al.* and Kurane *et al.* teach that GM-CSF elicits antitumor effects and because the retroviral vectors of Hall-1, Hall-2, Liu *et al.* and Gordon *et al.* were designed for targeted delivery of therapeutic genes to tumors. Applicant respectfully traverse this rejection.

Relevant Law

[I]n order to establish a prima facie case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of

generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The Claims

See above.

Differences between the teachings of the cited references and the claimed subject matter

The Primary References

Hall-1 (WO 98/44938)

Hall-1 teaches a viral vector particle having a modified viral surface protein wherein the viral surface protein is modified to include a targeting polypeptide including a binding region which binds to an extracellular matrix component. Hall-1 teaches a modified retroviral targeting polypeptide comprising the collagen-binding domain of von Willebrand factor. Hall-1 also teaches a therapeutic gene encoded by the viral particle, including a cytokine such as GM-CSF, and methods of delivery and treatment of diseases and disorders associated with exposed extracellular matrix components, including cancer. Hall-1 does not teach or suggest actively recruiting host mononuclear cells to the site of tumor as a result of expression of GM-CSF from cells of a tumor transduced by targeted retroviral particles comprising a modified surface protein

for targeting to the extracellular matrix or tumor vasculature of a tumor and a gene encoding GM-CSF.

Hall-2 (Human Gene Therapy 11:983-993 (2000))

Hall-2 teaches retroviral vectors bearing chimeric envelope proteins comprised of von Willebrand factor-derived matrix-binding sequences capable of transducing cells resulting in expression of a reporter gene (β-galatosidase). Hall-2 teaches transduction of tumor foci (approximately 1-3%) as detected by reporter gene expression after portal vein infusion of a matrix-targeted vector in a nude mouse model of liver metastasis. Hall-2 suggests that targeted injectable retroviral vectors would be suitable for improving therapeutic gene delivery in numerous clinical applications, including metastatic cancer. Hall-2 does not teach or suggest retroviral vectors encoding cytokines and modified surface proteins for targeting to extracellular matrix for transduction of tumors wherein host mononuclear cells are recruited to the site of the tumor upon expression of GM-CSF from transduced tumor cells.

Gordon *et al.*

Gordon *et al.* teaches inhibition of tumor growth via expression of cytocidal cyclin G1 in tumor cells transduced with retroviral vectors bearing chimeric envelope proteins comprising collagen-binding polypeptides for targeting to extracellular matrix components. Gordon *et al.* teaches antiproliferation of tumor cells resulting from cytocidal gene expression from transduced tumor cells. Gordon *et al.* does not teach or suggest reducing tumor mass by actively recruiting host mononuclear cells to the site of tumor in response to cytokine expression from cells of a tumor transduced by retroviral particles comprising modified surface proteins for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a GM-CSF gene.

Liu *et al.*

Liu *et al.* teaches a retroviral vector particle comprised of surface proteins that incorporate tumor vasculature targeting motifs into moloney murine leukemia virus env escort proteins that enhance retrovirus binding and transduction of human endothelial cells. Liu *et al.* does not teach a retroviral particle comprising a modified surface protein including a von Willebrand factor collagen binding motif for targeting to tumor vasculature or extracellular

matrix of a tumor to transduce cells of the tumor and actively recruit host mononuclear cells to the site of tumor in response to cytokines expressed from tumor cells transduced by the retroviral particle.

The Secondary References

As described in detail below, neither of the secondary references, alone or together, cure the defects in the primary references. The primary references do not teach or suggest recruitment of host mononuclear cells to the site of a tumor. The secondary references do not cure this defect.

Borrello *et al.*

Borrello *et al.* teaches generating a GM-CSF-producing bystander cell line for use in antitumor vaccine development. Borrello *et al.* teaches that delivering GM-CSF to the animal with a mixture of autologous tumor cells and the GM-CSF-producing bystander cells primes antitumor immune responses that are equivalent or better than those achieved using autologous tumor cells directly transduced to secrete GM-CSF. Borrello *et al.* does not teach or suggest recruiting host mononuclear cells in response to GM-CSF expression from cells of a tumor transduced by targeted retroviral vectors comprising modified surface proteins for targeting to extracellular matrix components or tumor vasculature of a tumor and a gene encoding GM-CSF.

Kurane *et al.*

Kurane *et al.* teaches methods of delivering cytokines to an animal as an adjuvant for priming lymph node cells draining sites for vaccine inoculation for the purposes of generating immune cells for adoptive immunotherapy. Kurane *et al.* teaches that local delivery of GM-CSF by autocrine or paracrine secretion of genetically engineered cells, as well as direct intratumoral delivery was capable of enhancing the antitumor reactivity of vaccine-primed lymph node cells as compared to systemic adminstration, which did not. Kurane *et al.* does not teach actively recruiting host mononuclear cells to the site of tumor in response to GM-CSF expression from cells of a tumor transduced by retroviral particles comprising a modified surface protein for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a GM-CSF gene.

The combination of teachings of the cited references does not result in any of the instantly claimed elements

The Examiner has rejected claims 1, 3, 9 and 10 as being obvious to an artisan of skill to modify the vector(s) of Hall-1, Hall-2, Liu et al, and Gordon *et al.* by cloning the GM-CSF encoding sequences taught by Borrello *et al.* with reasonable expectation of success and use the resultant vector for delivering GM-CSF to a tumor in an animal.

As described in detail above, none of the references alone or in combination teach or suggest recruitment of host mononuclear cells to the site of tumor in an animal in response to GM-CSF expression from cells of a tumor transduced by targeted retroviral particles as instantly claimed.

As indicated by the Examiner in the Final Office Action dated December 28, 2004, "Applicants arugments that expression of GM-CSF at tumor locations resulted in reduced tumor mass". The Examiner indicates that the arguments were found unpersuasive as being irrelevant to the pending claims. The Examiner then states: "...applicants have argued of un-expected result of recruitment of host mononuclear cells to the site of tumor. It is noted that this result is irrelevant to the instantly presented claims because no such limitation is recited in the claims."

As amended herein, Claim 1 now recites "recruitment of host mononuclear cells to the site of the tumor." The instant claims thus provide for a retroviral particle comprising a modified surface protein for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a GM-CSF gene for transduction of cells of a tumor, wherein expression of GM-CSF results in the recruitment of host mononuclear cells to the site of the tumor, when the retroviral particle is adminstered to a subject as a pharmaceutical composition in an effective amount for the treatment of cancer. As indicated by the Examiner, experiments performed by the Applicants demonstrating the recruitment of host mononuclear cells to the site of tumor after transduction with the instantly claimed targeted retroviral particles was "un-expected". Therefore, following the teachings of the references alone or in combination would not result in the elements as instantly claimed. Therefore, the instant claims are not obvious over the teachings of the cited references.

The combination of teachings does not result in the instantly claimed subject matter that includes the element of host mononuclear cell recruitment to the site of tumor in response to GM-CSF expression from cells of a tumor transduced by the instantly claimed retroviral particles. None of the cited art teaches, suggests or mentions a retroviral particle targeted to extracellular matrix or tumor vasculature of a tumor encoding a gene for GM-CSF for transduction of tumor cells to recruit host mononuclear cells to the site of tumor for the treatment of cancer. The rejection of claims 1, 3, 9, and 10 as being unpatentable under 35 U.S.C. §103(a) in view of the cited references is respectfully traversed.

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In view of the above amendments and remarkes, reconsideration and allowance of the application are respectfully requested. Please direct all charges and credit any overpayments in connection with this paper to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2/28/05

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